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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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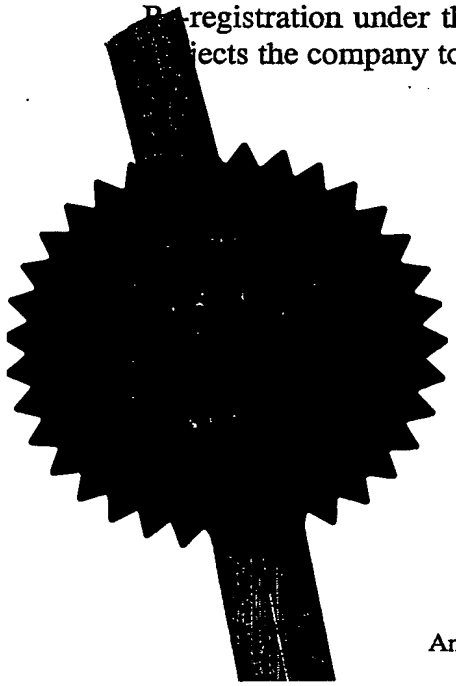
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 20 January 2003

PCT/GB 03/03215

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P01/7700 0.00-0207495.3

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
28 MAR 2002
NEWPORT

The **Patent Office**

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

28 MAR 2002

The Patent Office
Cardiff Road
Newport
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1.	Your reference	G-32413P1/BCK 9916
2.	Patent application number *(The Patent Office will fill in this part)*	0207495.3
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	BIOCHEMIE GESELLSCHAFT MBH A-6250 KUNDL/TIROL AUSTRIA
	Patent ADP number *(if you know it)*	8355158001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	23
Claim(s)	3 DML
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE ✓
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A Yorke + Co — Date: 28 March 2002

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

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d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

Organic Compounds

The present invention relates to organic compounds, such as compounds which are active in the treatment of diseases caused by *Mycobacterium*.

Tuberculosis is a chronic infectious disease caused by infection with *Mycobacterium tuberculosis*. Tuberculosis is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If untreated, serious complications and death typically result. Tuberculosis may be generally controlled by antibiotic therapy, such as by treatment with Isoniazid, see e.g. The Merck Index, 12th edition, item 5203; Rifampin (Rifampicin®), see e.g. The Merck Index, 12th edition, item 8382, Streptomycin, see e.g. e.g. The Merck Index, 12th edition, item 8983; but a major problem is the development of strains of drug resistance against such antibiotics.

We have now found that a compound class which is known to have antibiotic activity shows surprisingly activitiy in the treatment of diseases caused by *Mycobacterium*, even against drug resistant strains.

In one aspect the present invention provides the use of a pleuromutilin in the preparation of a medicament for the treatment of diseaeses caused by *Mycobacterium*.

In another aspect the present invention provides a method of preventing or treating diseases caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective, e.g. an anti-mycobacterium effective; amount of a pleuromutilin.

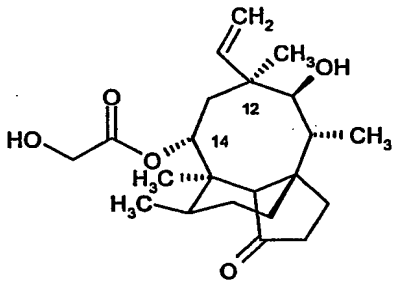
Mycobacterium includes *M tuberculosis.* Diseaeses caused by *Mycobacterium* include mycobacterium infections. A pleuromutilin includes one or more pleuromutilins.

A pleuromutilin for use according to the present invention or for treating or preventing diseases according to the present invention is designated hereinafter as "a pleuromutilin of the present invention".

A pleuromutilin of the present invention includes a pleuromutilin in the form of a free base, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate, e.g. and in the form of a complex, such as a cyclodextrin complex.

A pleuromutilin of the present invention may exist in the form of isomers and mixtures thereof, e.g. including diastereoisomers and mixtures thereof. Isomeric or diastereoisomeric mixtures may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers or diastereoismers, respectively. The present invention includes a pleuromutilin according to the present invention in any isomeric and diasteroisomeric form and in any isomeric and diastereoisomeric mixture. Preferably the cofiguration in the mutilin ring is the same as in a naturally produced mutilin.

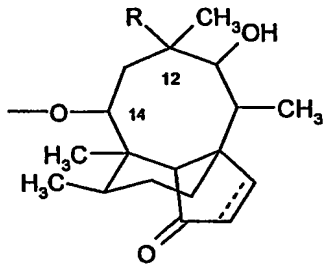
Pleuromutilin, a compound of formula



A

is a naturally occurring antibiotic, e.g. produced by the basidomycetes *Pleurotus mutilus* and *P.passeckerianus*, see e.g. The Merck Index, 12th edition, item 7694.
A number of further pleuromutilins having the principle ring structure of pleuromutilin and having e.g. antibacterial activity have been developed.

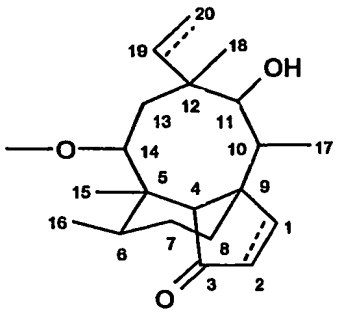
A pleuromutilin of the present invention includes a pleuromutilin having the basic structural elements as set out in formula



PLEU

wherein R is vinyl or ethyl and the dotted line is a bond or is no bond.

The following numbering system is used in the present application:

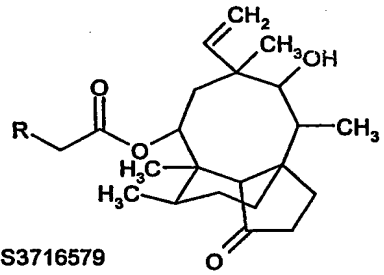


PLEU

The dotted line between positions 19 an 20 (and between positions 1 and 2) is a bond or is no bond. If the dotted line between positions 1 and 2 is no bond the ring system may be further substituted in positions 1 and 2. The group -O- in position 14 is further substituted, preferably by a substituted carbonyl group.

Examples of pleuromutilins according to the present invention includes e.g.

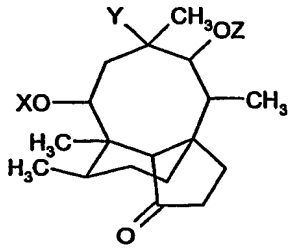
- A compound as disclosed in US3716579, e.g. of formula



I-US3716579

wherein R is CH_3-$(CH_2)_7$-CH=CH-$(CH_2)_7$-COO-, CH_3-$(CH_2)_4$-CH=CH-CH_2-CH=CH-$(CH_2)_7$-COO-, CH_3-$(CH_2)_9$-CH=CH-$(CH_2)_7$-COO- or hydrogen;

- A compound as disclosed in GB1312148, e.g. of formula



I-GB1312148

wherein X, Y and Z are as defined in any one of the following groups:

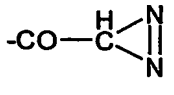
a. X is -CO-CH_2-R_1, wherein R_1 is H, Cl, Br, I, thiocyanato, azido, (N,N-tetramethylene-thiocarbamoyl)-mercapto, dithiocarbonic acid-O-(C_{1-3})alkyl, -S-phenyl, S-phenyl substituted by carboxyl or by one or two OH, -S-pyridyl, -S-benzyl, -S-(C_{1-5})alkyl, or -S-(C_{1-5})alkyl substituted by one or more amino, OH or carboxyl, Y is vinyl, and Z is H;

b. X is CO-CO-OH, Y is vinyl and Z is H;

c. X is $COCH_3$, Y is vinyl and Z is H;

d. X is $COCH_2NH_2$, Y is ethyl and Z is H;

e. X is a group of formula

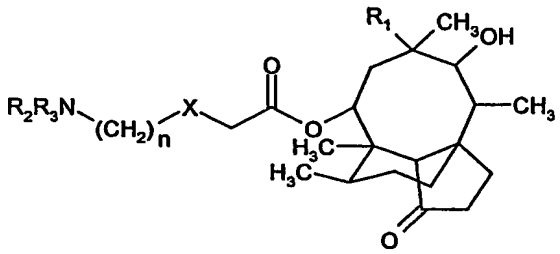


, Y is ethyl and Z is H

f. X is H, Y is vinyl and Z is acetyl; or

g. X is COR_2, wherein R_2 is (C_{1-5})alkyl, Y is vinyl and Z is H,

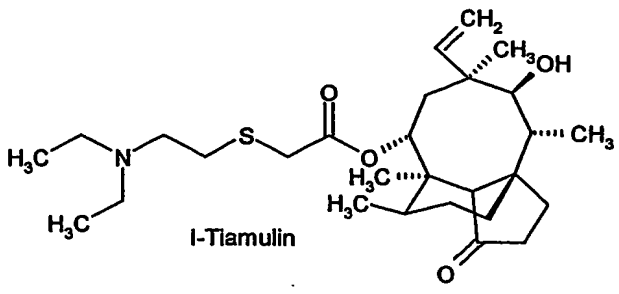
- A compound as disclosed in US4278674, e.g. of formula



I-US4278674

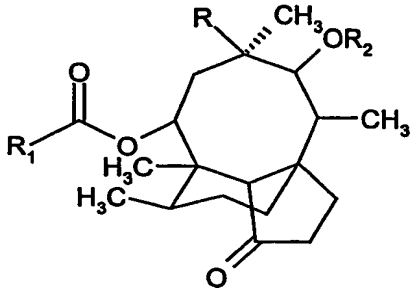
wherein R_1 is vinyl or ethyl, n is an integer from 2 to 5, X is sulphur or a group -Y-phenylene-Z- or a group $=NR_4$, Y and Z are both sulphur or one of Y and Z is sulphur and the other is oxygen, R_4 is H or a second mutilin ring of formula US4278674, wherein R_1 is as defined above and attached via a $-O-CO-CH_2-$ group in position 14; each of R_2 and R_3 is (C_{1-10})alkyl, or R_2 and R_3 together with the nitrogen atom form pyrrolidino, piperidino, morpholino, thiomorpholino, or 1-hexahydro-1H-azepino, or R_2 and R_3 together with the nitrogen atom form piperazinyl, the second nitrogen atom of which is substituted by (C_{1-5})alkyl, (C_{1-4})hydroxyalkyl, (C_{2-5})alkynoyloxy(C_{1-4})alkyl, or benzoyloxy(C_{1-4})alkyl, or R_1 is as defined above, n = 2, R_3 is (C_{1-10})alkyl, (C_{1-4})hydroxyalkyl, (C_{2-5})alkynoyloxy-(C_{1-4})alkyl, or benzoyloxy(C_{1-4})alkyl, X is $=NR'_4$ and R_2 together with R'_4 forms an ethylene bridge between both nitorgen atoms; such as

- 14-Desoxy-14[(2-diethylaminoethyl)mercaptoacetoxy]mutilin, e.g. also known as tiamulin of formula



I-Tiamulin

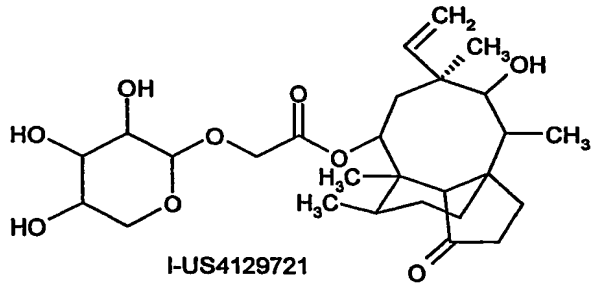
- A compound as disclosed in US4130709, e.g. of formula



I-US4130709

wherein R is ethyl or vinyl, R_1 is selected from α- or β-anomers of hexopyranoses, hexofuranoses, pentopyranoses, pentofuranoses, pyranose and furanose aminosugars, disaccharides, trisaccharides and R_2 is H, benzoyl or (C_{2-4})alkanoyl; or R_1 is 2-deoxy-2-(hydroxyimino)-3,4,6-tri-O-acetyl-α-D-glucopyranosyl or -galactopyranosyl, 2-deoxy-2-(hydroxyimino)-α-D- galactopyranosyl, 2-deoxy-2-amino-4,6-di-O-acetyl-α-D-glucopyranosyl, or 2-deoxy-2-acetamido-3,4,6-tri-O-acetyl-α-D-glucopyranosyl and R_2 is H;

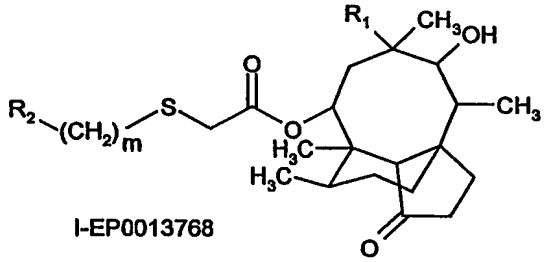
- A compound as disclosed in US4129721; e.g. of formula



I-US4129721

and the 19,20-dihydro derivative thereof and the tetra (C_{2-6})alkanoyl derivatives thereof;

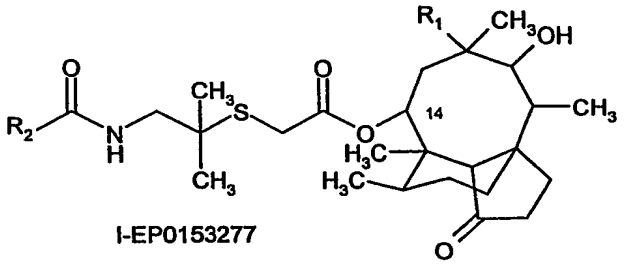
- A compound as disclosed in EP0013768, e.g. of formula



I-EP0013768

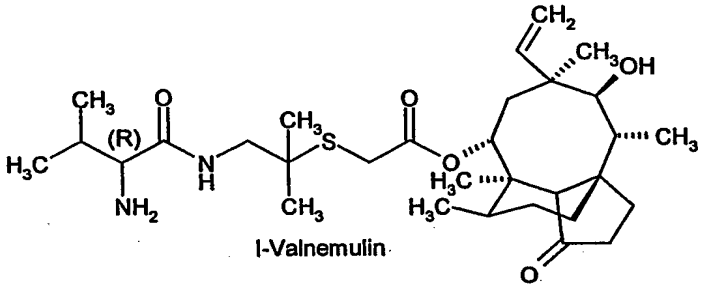
wherein R_1 is vinyl or ethyl, m is 0 or 1, and R_2 is a heterocyclic radical, in which a 5- or 6-membered, unsaturated or saturated heterocyclic ring containing one or more hetero atoms selected from O, S and N, is attached to the $-S(CH_2)_m-$ group;

- A compound as disclosed in EP0153277, e.g. an N-acyl-14-O-[(1-amino-2-methylpropan-2-yl)thioacetyl]-mutilin or 19,20-dihydromutionin,such as of formula



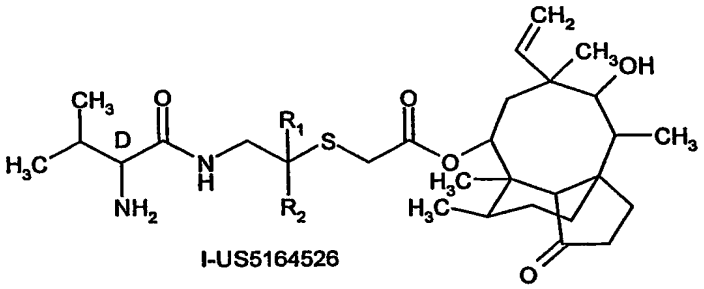
I-EP0153277

wherein R_1 is vinyl or ethyl, and R_2 is optionally hydroxy-substituted aminoalkyl or a 5-membered saturated heterocycle, e.g. including Valnemulin (Econor®) of formula



I-Valnemulin

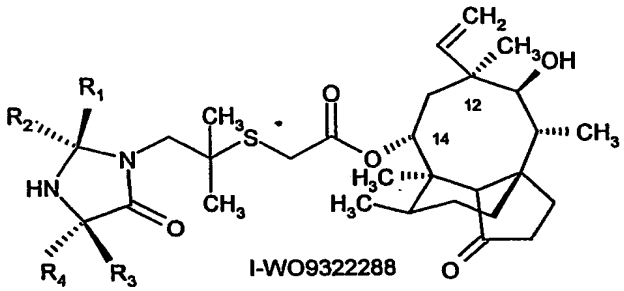
- A compound as disclosed in US516526, e.g. of formula



I-US5164526

wherein R_1 and R_2 independently of each other are H, alkyl, alkenyl, cycloalkyl, aryl or aralkyl;

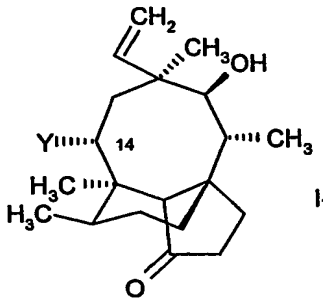
- A compound as disclosed in WO9322288, e.g. of formula



I-WO9322288

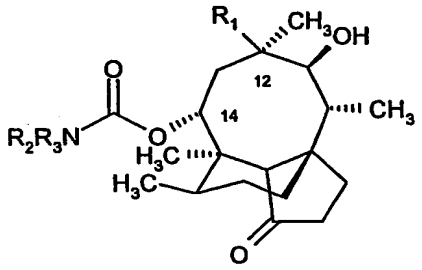
wherein R_1 and R_2 are independently of each other H, alkyl, or, R_1 and R_2 together with the carbon atom to which they are attached are cycloalkyl; and R_3 and R_4 independently of each other are H, alkyl or substituted alkyl;

- A compound as disclosed in WO9725309, e.g. of formula



I-WO9725309

wherein Y is carbamoyloxy, wherein the N-atom is unsubstituted or mono- or disubstituted, such as a compound of formula



II-WO9725309

wherein R_1 is vinyl or ethyl, R_2 and R_3 independently of each other are H, or optionally substituted

- saturated or unsaturated (C_{1-6}) hydrocarbon or (C_{3-8})cyclic hydrocarbon,
- heterocyclyl or aryl, or

R_2 and R_3 together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group; or

R_2 is one of the above monovalent groups and and R_3 is a group selected form SO_2R_4, COR_5, OR_5 and NR_6R_7; wherein

R_4 is optionally substituted,

- saturated or unsaturated (C_{1-6})hydrocarbon or (C_{3-8})cyclic hydrocarbon,
- heterocyclyl, aryl, (C_{1-6})alkylamino or arylamino;

R_5 is optionally substituted

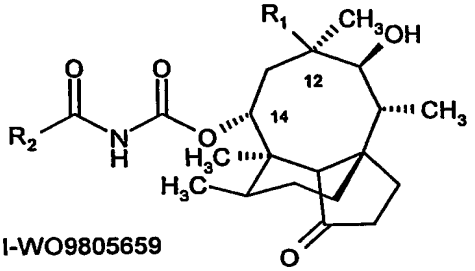
- saturated or unsaturated (C_{1-6}) hydrocarbon or (C_{3-8})cyclic hydrocarbon,
- heterocyclyl or aryl,

R_6 and R_7 independently of each other are H, or optionally substituted

- saturated or unsaturated (C_{1-6}) hydrocarbon or (C_{3-8})cyclic hydrocarbon,
- heterocyclyl or aryl, or

R_6 and R_7 together with the nitrogen atom to which they are attached form an optionally substituted (C_{3-8})cyclic group, optionally containing one additional heteroatom selected from N, O or S, and optionally fused to a hydrocarbon ring, a heterocyclic ring or an aromatic group;

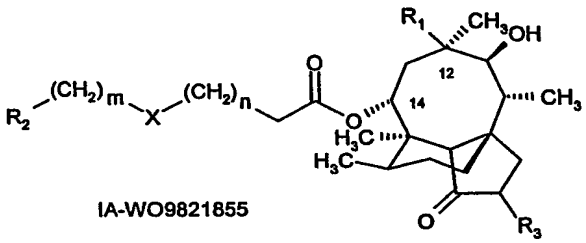
- A compound as disclosed in WO9805659, e.g. of formula



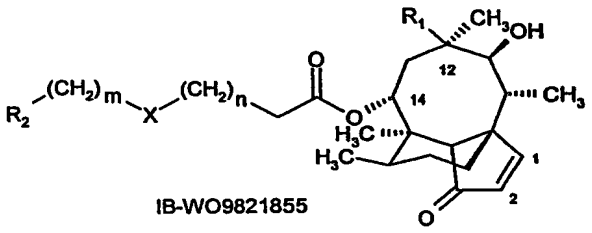
I-WO9805659

wherein R_1 is vinyl or ethyl, and R_2 is a group R_3, R_4CH_2-, or R_5R_6CH=CH-, wherein , each of R_3 and R_4 is an azabicyclic ring system, or R_5 and R_6 together with the carbon atom to which they are attached form an azabicyclic ring system;

- A compound of WO9821855; e.g. of formula



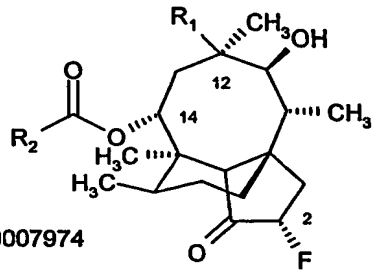
IA-WO9821855



IB-WO9821855

wherein n and m are independently of each other 0, 1 or 2; X is O, S, S(O), SO_2, -COO-, -NH-,-CONH-, -NHCONH-, or a bond; R_1 is vinyl or ethyl; R_2 is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen atoms and attached through a ring carbon atom, e.g. R_2 is optionally substituted quinuclidinyl, azabicyclo[2.2.1]heptyl, azabicyclo[4.3.0]nonyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.0]octyl, azabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octenyl, azabicyclo[3.3.1]nonyl or azabicyclo[4.4.0]decyl; R_3 is H, OH; or the moietity $R_2(CH_2)_mX(CH_2)_nCH_2COO$ at position 14 of IA or IB is replaced by R_aR_bC=CHCOO, wherein one of R_a or R_b is hydrogen and the other is R_2; or R_a and R_b together form R_2;

- A compound as disclosed in WO0007974, e.g. a 14-acyloxy derivative of mutilin or 19,20-dihydromutilin having a 2-fluoro substituent, such as of formula



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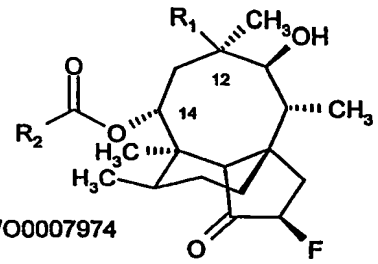
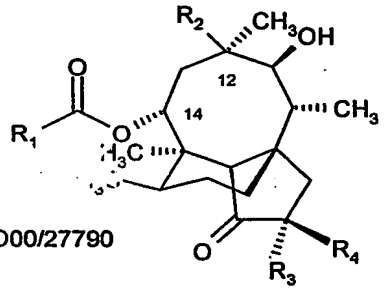


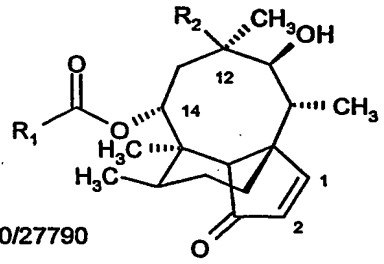
IB-WO0007974

wherein R_1 is vinyl or ethyl, and R_2COO- is acyloxy, e.g. $HOCH_2CO_2$- or R-X-CH_2CO_2, wherein X is O, S or NR' and R and R' are indpendently of each other an aliphatic or aromatic group, preferably R_2COO- is a carbamoyl group, such as a group $R_3R_4NCO_2$- wherein R_3 and R_4 have various meanings (e.g. R_3 and R_4 have the meaning as disclosed for the meaning of R_2 and R_3 in WO9725309);

- A compound as disclosed in WO0027790, e.g. a compound of formula

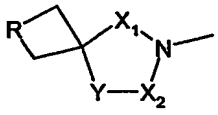


IA-WO00/27790



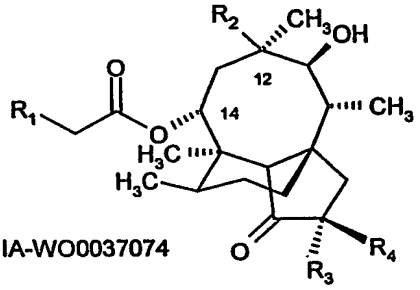
IB-WO00/27790

wherein R_1 is a $R^A(CH_2)nO(CH_2)_m$, $R^A(CH_2)_p$, or a group of formula

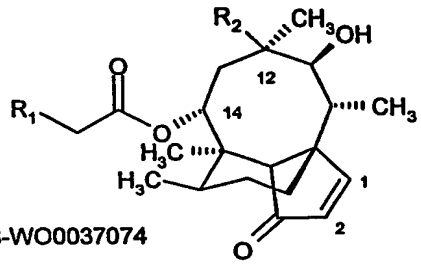


wherein R is a spiro-fused mono- or bicyclic ring containing one or two basic N-atoms; X_1 and X_2 which may be the same or different, are each -CH_2- or -C=O, provided that at least one of X_1 and X_2 is -C=O; and Y is -NH-, -CH_2- or -CH_2-CH_2-; R^A is an optionally substituted aryl group or heteroaryl group linked via a carbon atom; e.g. R^A is optionally substituted phenyl, thienyl, pyridinyl, furyl, thiazolyl, isoxazolyl, benzimidazolyl, quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl or benzthiazolyl: m is 1, 2 or 3; n is 0, 1 or 2; p is 1 to 4; R_2 is vinyl or ethyl; and R_3 is H, OH or F, and R_4 is H; or R_3 is H and R_4 is F;

- A compound as disclosed in WO0037074, e.g. a compound of formula



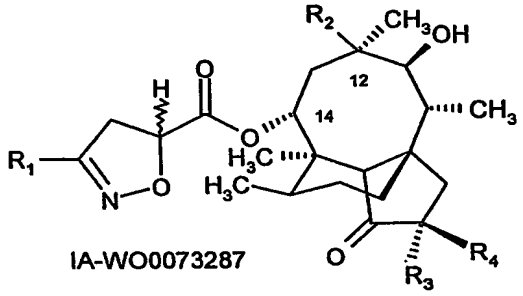
IA-WO0037074



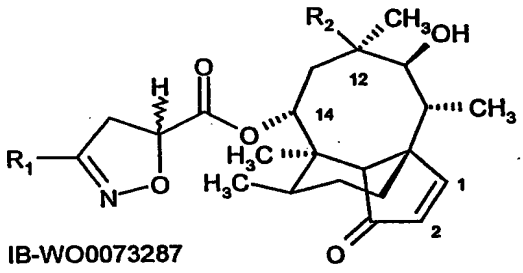
IB-WO0037074

wherein R_1 is an optionally substituted heteroaryl group which comprises a 5-membered heteroaromatic ring which has at least one N-atom, e.g. a pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, indole, benzimidazole, benzotriazole, 2-aza-indole or 6-aza-indole; and which is linked via a N-atom; R_2 is vinyl or ethyl; R_3 is H, OH or F, and R_4 is H; or R_3 is H and R_4 is F;

- A compound as disclosed in WO0073287, e.g. a compound of formula



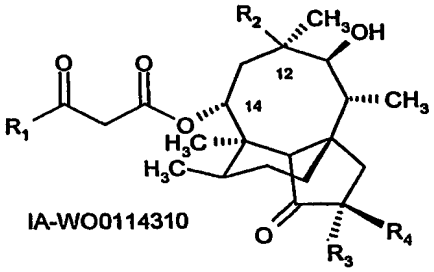
IA-WO0073287



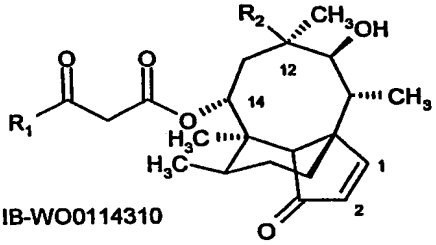
IB-WO0073287

wherein R_1 is optionally substituted aryl, e.g. azabicyclo-octyl; or an optionally substituted nitrogen containing ring, e.g. piperidinyl; R_2 is vinyl or ethyl; R_3 is H, OH or F and R_4 is H; or R_3 is H and R_4 is F;

- A compound as disclosed in WO0114310, e.g. a compound of formula



IA-WO0114310



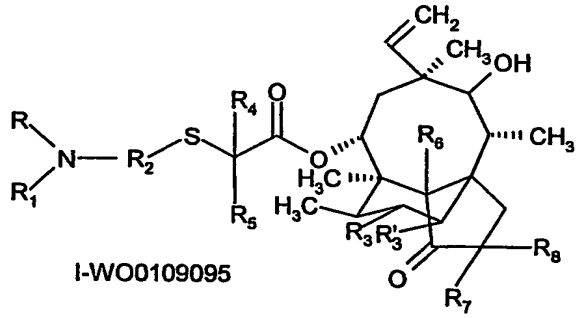
IB-WO0114310

wherein R_1 is a nitrogen containing heterocycle, an optionally substituted aryl or optionally subsituted heteroaryl, or CH_2R_5,

e.g. R_1 is optionally substituted phenyl, 3-pyridyl, 4-pyridyl, pyrimidin-2-yl, 1,3,4-thiadiazol-2-yl, benzothiazol-2-yl. 2H-1,2,4-triazol-3-yl, azabicycloheptyl, azabicyclooctyl or piperidinyl;

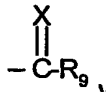
R_2 is vinyl or ethyl; R_3 is H, OH or F and R_4 is H; or R_3 is H and R_4 is F; R_5 is halogen or SR_6; and R_6 is aminoalkyl, a nitrogen containing heterocycle, or an optionally substituted aryl or optionally subsituted heteroaryl; e.g. R_6 is optionally substituted phenyl, 3-pyridyl, 4-pyridyl, pyrimidin-2-yl, 1,3,4-thiadiazol-2-yl, benzothiazol-2-yl. 2H-1,2,4-triazol-3-yl, azabicycloheptyl, azabicyclooctyl or piperidinyl;

- A compound as disclosed in WO0109095, e.g. a compound of formula

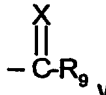


I-WO0109095

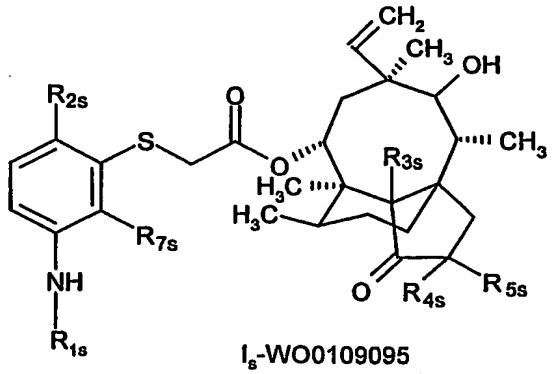
wherein R is hydrogen or alkyl; R_1 is hydrogen or a group of formula



wherein X is S, O, or NR_{10}, wherein R_{10} is H or alkyl, or $N^+(R'_{10})$, wherein R'_{10} is alkyl in the presence of an appropriate anion; and R_9 is amino, alkyl, aryl, heterocyclyl or mercapto; and, if X is oxygen, R_9 is additionally hydrogen; R_2 is arylene, e.g. phenylene; or heterocyclene; R_4 is hydrogen or alkyl; R_5 is hydrogen or alkyl; R_3, R_3', R_6, R_7 and R_8 independently of each other are hydrogen or deuterium; or R and R_2 together with the nitrogen atom to which they are attached form non-aromatic heterocyclene and R_1 is a group of formula

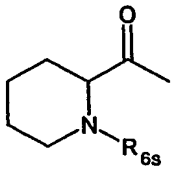


wherein X and R_9 are as defined above; e.g. a compound of formula



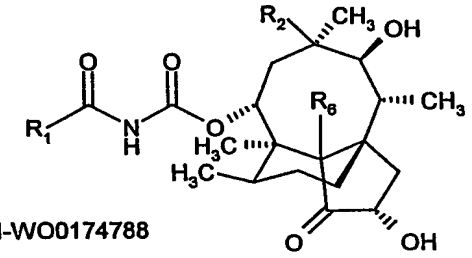
I_s-WO0109095

wherein R_{1s} is hydrogen or a group of formula



wherein R_{6s} is hydrogen or deuterium; R_{2s} is hydrogen, methyl or tert-butyl; R_{7s} is hydrogen or methyl; and R_{3s}, R_{4s} and R_{5s} are hydrogen or deuterium;

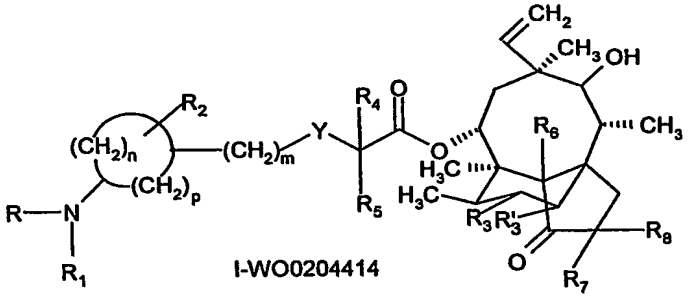
- A compound as disclosed in WO0174788, e.g. a compound of formula



I-WO0174788

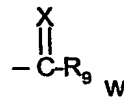
wherein R_1 is a 5- or 6-membered optionally substituted heteroaryl group; e.g. pyridine, pyridazine, pyrimidine, pyrazine, isoxazole, thiazole, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, benzimidazole, 3-oxo-3,4-dihydropyrido[2,3-b]pyrazine, or pyrazolo[1,5-a]pyrimidine; and R_2 is vinyl or

- A compound as disclosed in WO0204414, e.g. a compound selected from 14-O-[(cycloalkyl-sulfanyl)acetyl]mutilins; 14-O-[(cycloalkyl-alkyl-sulfanyl)acetyl] mutilins; 14-O-[(cycloalkoxy)acetyl]mutilins; or 14-O-[(cycloalkyl-alkoxy)acetyl] mutilins, such as of formula

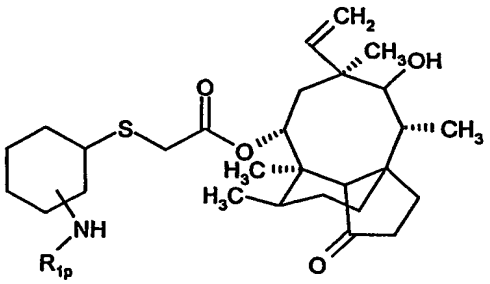


I-WO0204414

wherein R is hydrogen; R_1 is hydrogen or a group of formula



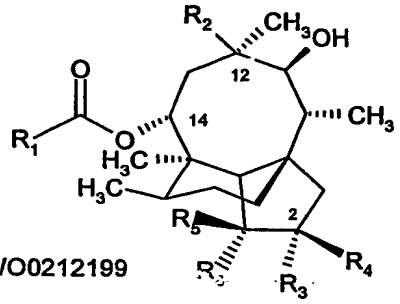
wherein X is sulphur, oxygen or NR_{10}, wherein R_{10} is hydrogen or alkyl; and R_9 is amino, alkyl, aryl or heterocyclyl; and, if X is oxygen, R_9 is additionally hydrogen; Y is sulphur or oxygen; R_2 is hydrogen or one or more substituents, R_4 is hydrogen or alkyl; R_5 is hydrogen or alkyl; R_3 and R_3' are hydrogen, deuterium, or halogen; R_6, R_7 and R_8 are hydrogen or deuterium; m is a number selected from 0 to 4; n is a number selected from 0 to 10; and p is a number selected from 0 to 10; with the proviso that n plus p are at least 1; e.g. a compound of of formula



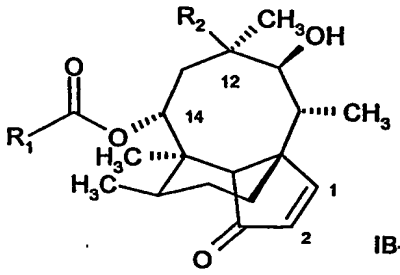
I_p-WO0204414

wherein R_{1p} is hydrogen or the residue of an amino acid;

- A compound as disclosed in WO0212199, e.g. a compound of formula



IA-WO0212199



IB-WO0212199

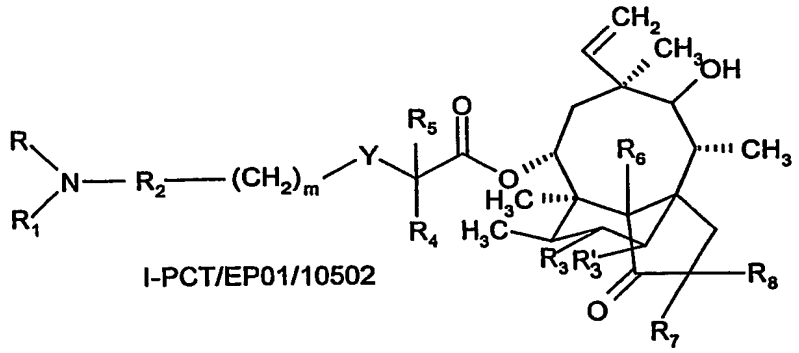
wherein R_1 is:

- a 5- or 6-membered aromatic or heteroaromatic ring attached via a ring carbon atom, preferably pyridyl, and comprising a substituent selected from halo, R_7O-, R_7S- or R_8R_9N- on a ring carbon adjacent to the carbon of attachment; or
- a 5- or 6-membered dihydro heteroaromatic ring attached via a ring carbon atom and comprising one oxygen or one or two nitrogen atoms and optionally fused to phenyl, a 5- or 6-membered heteroaryl ring comprising one or two nitrogen atoms or a 5- or 6-membered heterocyclyl ring comprising a sulphur, oxygen or nitrogen atom and further comprising a substituent selected from oxo or thioxo on a ring carbon adjacent to the carbon of attachment;
- a 6-membered tetrahydro heteroaromatic ring attached via a ring carbon atom comprising one or two nitrogen atoms and further comprising two substituents independently selected from oxo or thioxo wherein one of the substituents is on a ring carbon adjacent to the carbon of attachment; or
- a bicyclic heteroyaryl ring attached via a ring carbon atom and comprising nine or ten ring atoms and from one to four nitrogen atoms;

wherein the ring of R_1 may be optionally further substituted; R_2 is vinyl or ethyl; R_3 is H, OH or F and R_4 is H, or R_3 is H and R_4 is F; and R_5 and R_6 together form an oxo group; or R_3

and R_4 is each H and R_5 is H, or OH and R_6 is H, or R_5 is H and R_6 is H or OH; R_7 is optionally substituted (C_{1-6})alkyl; and R_8 and R_9 are independently selected from hydrogen or optionally substituted (C_{1-6})alkyl.

- A compound as disclosed in not yet published PCT-application PCT/EP01/10502, of formula

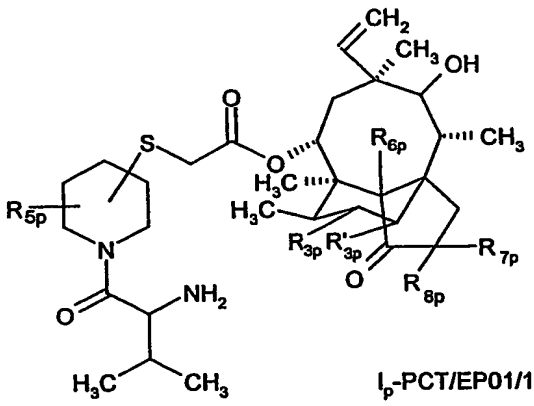


I-PCT/EP01/10502

wherein R and R_2 together with the nitrogen atom to which they are attached form pyrrolidinyl or piperidinyl, R_1 is a group of formula

, R_3 and R'_3 are hydrogen, deuterium or halogen, R_4 is hydrogen or alkyl, R_5 is hydrogen or alkyl, R_6, R_7 and R_8 are hydrogen or deuterium; R_9 is amino, alkyl, aryl, heterocyclyl or mercapto; and, if X is oxygen, R_9 is additionally hydrogen; R_{10} is hydrogen or alkyl, R'_{10} is alkyl, X is sulphur, oxygen, NR_{10}, or $N^+(R'_{10})_2$ in the presence of an appropriate anion, Y is sulphur or oxygen, and m is 0, 1 or 2;

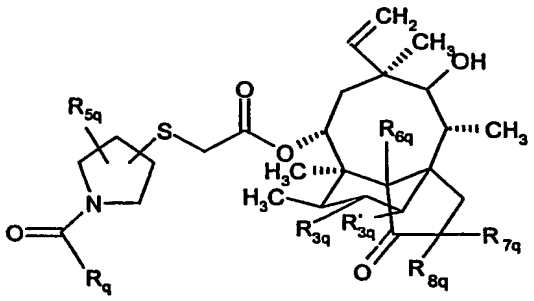
with the proviso that, when R and R_2 together with the nitrogen atom to which they are attached form piperidinyl, m is 0, Y is S and Y is attached in position 3 of said piperidine ring that group of formula I which is attached to the piperidine ring via the residue Y is either in the (S)-configuration or in the (R)-configuration, preferably in the (S)-configuration; preferably a compound of of formula



I_p-PCT/EP01/10502

wherein R_{3p}, R'_{3p}, R_{6p}, R_{7p} and R_{8p} are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for R_3, R'_3, R_6, R_7 and R_8; and R_{5p} is hydrogen or one or more substituents, and if the group attached to the piperidine ring via the sulphur atom is in position 3 of said piperidine ring and R_{5p} is hydrogen, then the group attached to the sulphur atom is either in the (S)-configuration or in the (R)-configuration;

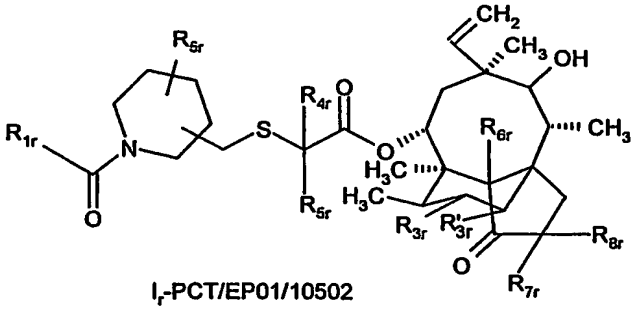
a compound of formula



I_q-PCT/EP01/10502

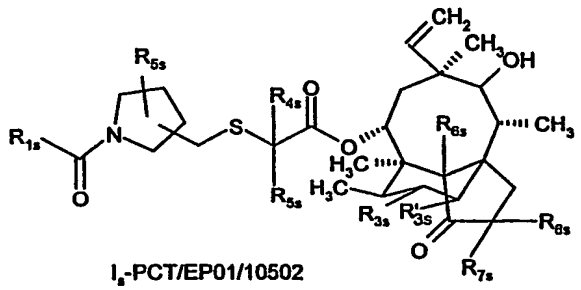
wherein R_{3q}, R'_{3q}, R_{6q}, R_{7q} and R_{8q} are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for R_3, R'_3, R_6, R_7 and R_8; R_{5q} is hydrogen or one or more substituents, preferably hydrogen; and R_q is that part of an amino acid which remains if the carboxylic group is splitt off;

a compound of formula



I_r-PCT/EP01/10502

wherein R_{3r}, R'_{3r}, R_{4r}, R_{6r}, R_{7r} and R_{8r} are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for R_3, R'_3, R_4, R_6, R_7 and R_8; R_{5r} is hydrogen or one or more substituents, and R_{1r} is that part of an amino acid which remains if the carboxylic group is splitt off, or a compound of formula



I_s-PCT/EP01/10502

wherein R_{3s}, R'_{3s}, R_{4s}, R_{6s}, R_{7s} and R_{8s}, respectively, are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for R_3, R'_3, R_4, R_6, R_7 and R_8; R_{5s} is hydrogen or one or more substituents, preferably hydrogen; and R_{1s} is that part of an amino acid which remains if the carboxylic group is splitt off; e.g. wherein in a compound of formula I_s the group attached to the piperidine ring via the sulphur atom is either in the (S)-configuration or in the (R)-configuration; e.g. wherein in a group R_{1s} the amine group of the amino acid residue is either in the (S)-configuration or in the (R)-configuration,

such as the compounds

14-O-[(N-(3-Methyl-2-amino-buturyl-piperidin-3(S)-yl)sulfanyl)acetyl]mutilin, e.g. including

14-O-[(N-(3-Methyl-2(R)-amino-buturyl-piperidin-3(S)-yl)sulfanyl)acetyl]mutilin; and

14-O-[(N-(3-Methyl-2(S)-amino-buturyl-piperidin-3(S)-yl)sulfanyl)acetyl]mutilin;

14-O-[(N-(3-Methyl-2-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin, e.g. including

14-O-[(N-(3-Methyl-2(R)-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin, and

14-O-[(N-(3-Methyl-2(S)-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin;

14-O-[(N-(3-Methyl-2-amino-butyryl)-piperidin-3-yl)-methylsulfanylacetyl]-mutilin, e.g. including

14-O-[(N-(3-Methyl-2-amino-butyryl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin, and

14-O-[(N-(3-Methyl-2-amino-butyryl)-piperidine-3(R)-yl)-methylsulfanylacetyl]-mutilin,such as

14-O-[(N-(3-Methyl-2(S)-amino-butyryl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin, and

14-O-[(N-(3-Methyl-2(R)-amino-butyryl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin;

14-O-[(N-(3-Methyl-2-amino-butyryl)-pyrrolidine-2-yl)-methylsulfanylacetyl]-mutilin, e.g. including

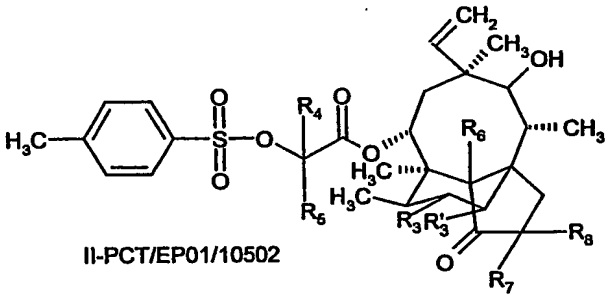
14-O-[(N-(3-Methyl-2-amino-butyryl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin, and

14-O-[(N-(3-Methyl-2-amino-butyryl)-pyrrolidine-2(S)-yl)-methylsulfanylacetyl]-mutilin, such as

14-O-[(N-(3-Methyl-2(R)-amino-butyryl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin and
14-O-[(N-(3-Methyl-2(S)-amino-butyryl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin,
14-O-[(N-(3-Methyl-2-amino-butyryl)-pyrrolidin-3-yl)sulfanylacetyl]mutilin, e.g. including
14-O-[(N-(3-Methyl-2(R)-amino-butyryl)-pyrrolidine-3-yl)-sulfanylacetyl]-mutilin and
14-O-[(N-(3-Methyl-2(S)-amino-butyryl)-pyrrolidine-3-yl)-sulfanylacetyl]-mutilin;
and
14-O-[(N-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin, e.g. including
4-O-[(N-(R)-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin, and
4-O-[(N-(S)-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin.
e.g. in free form or in the form of a salt, e.g. a salt with hydrochloric acid; such as a hydrochloride.
14-O-[(N-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin is 14-O-[(N-(3-(imidazol-4yl)-2-amino-propionyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin.

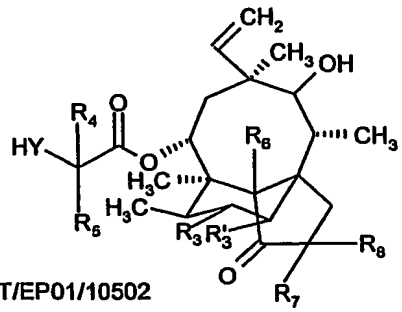
A compound of formula PCT/EP01/10502 may be obtained as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. by a process comprising the steps

a. reacting a compound of formula



II-PCT/EP01/10502

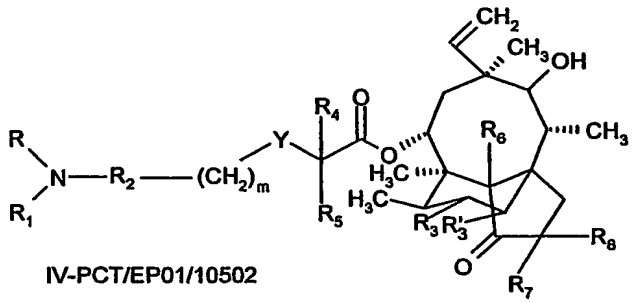
wherein R_3, R'_3, R_4 and R_5 are as defined in claim 1 of PCT/EP01/10502 and R_6, R_7 and R_8 are hydrogen, with urea or thiourea and subsequent reduction to obtain a compound of formula



III-PCT/EP01/10502

wherein Y is as defined in claim 1 of PCT/EP01/10502; R_3, R'_3, R_4 and R_5 are as defined above and R_6, R_7 and R_8 are hydrogen,

b. reacting a compound of formula III as defined in step a. with optionally substituted pyrrolidine, methyl or ethyl pyrrolidine, piperidine, methyl or ethyl piperidine (= methyl-, ethyl- pyrrolidine or piperidine), respectively, carrying at the nitrogen atom a group of formula $-C(=X)R_9$, wherein X and R_9 are as defined in claim 1 of PCT/EP01/10502, in the form of a reactive derivative, e.g. in the form of a mesylate or a tosylate; to obtain a compound of formula



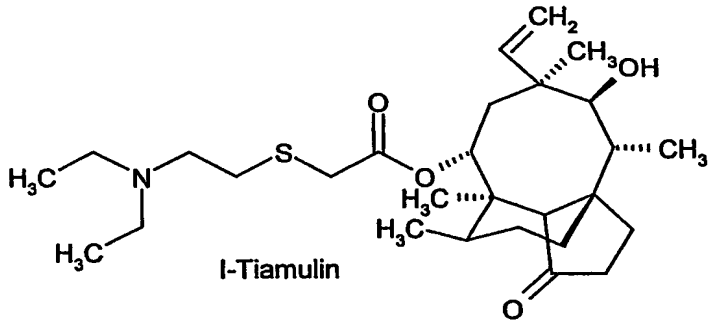
IV-PCT/EP01/10502

which is a compound of formula I of PCT/EP01/10502 wherein R, R_1, R_2, R_3, R'_3, R_4, R_5, Y and m are as defined in claim 1 of PCT/EP01/10502 and R_6, R_7 and R_8 are hydrogen; and, if desired,

c. introducing deuterium into a compound of formula IV as defined in step b, to obtain a compound of formula I, wherein R, R_1, R_2, R_3, R'_3, R_4, R_5, Y and m are as defined above and R_6, R_7 and R_8 are deuterium.

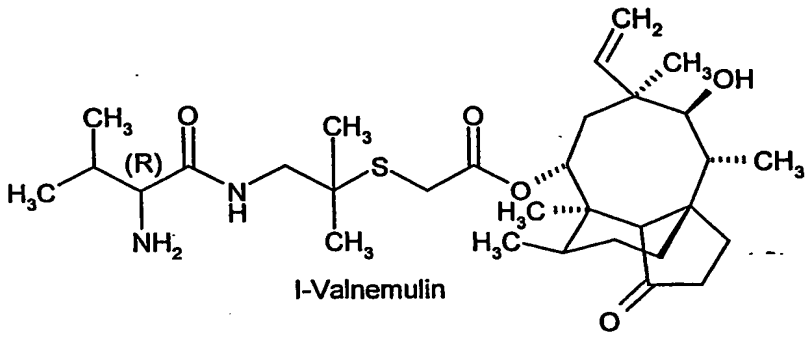
A pleuromutilin of the present invention is preferably a compound of formula US4278674, a compound of formula EP0153277, a compound of formula WO0109095, a compound of formula WO0204414 or a compound of formula PCT/EP01/10502, e.g. including

- a compound of formula



I-Tiamulin

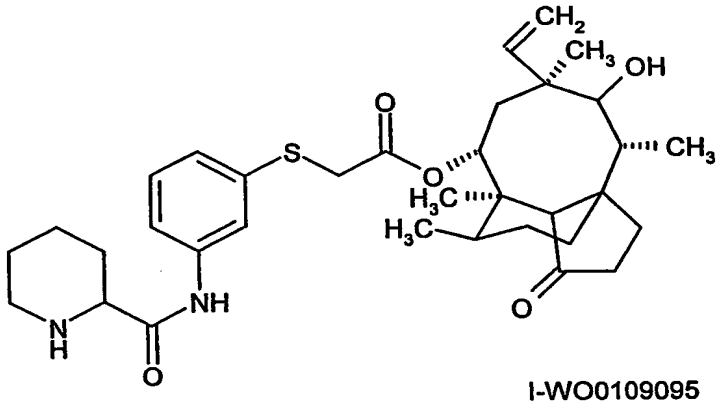
- a compound of formula



I-Valnemulin

e.g. in the form of a hydrochloride;

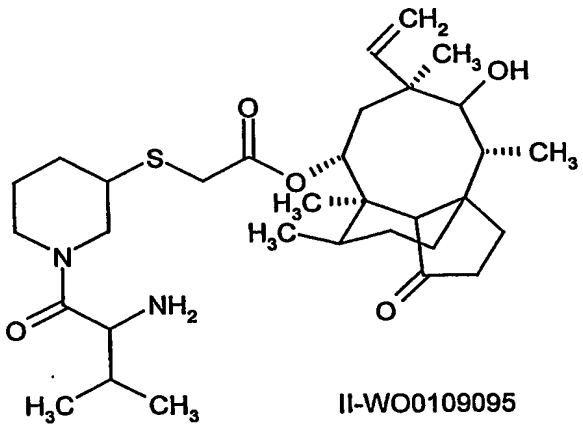
- a compound of formula



I-WO0109095

e.g. in the form of a hydrochloride;

- a compound of formula



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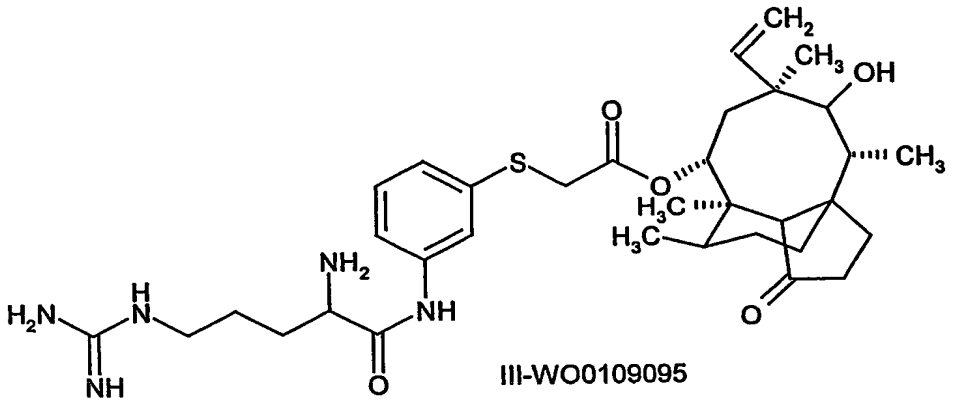
e.g. in the form of a hydrochloride; and

- a compound of formula



III-WO0109095

e.g. in the form of a hydrochloride.

Activity against strains of *Mycobacterium*, e.g. *M.tuberculosis* may be determined according to the following General Test Procedure:

General Test procedure

Is carried out according to the known and appropriate Agar Dilution Test.

Agar is used as a substrate. Shortly before solidifaction of the Agar TEST COMPOUNDS in different concentrations are added and mixed into the still liquid agar mass (according to the Agar dilution test). Controls without TEST COMPOUNDS are also prepared for determination of strain growth ability. The thus prepared agars are inoculated after solidification with *Mycobacterium tuberculosis* strains. Incubation is carried out in normal incubators at 37°C. As a nutrition medium Middlebrook 7H10 + OADC (Oleic, Albumin, Dextrose, Catalase) Enrichment (pH 6.71- 6.73) is used.

The minimum inhibition concentration (MIC) which is the compound concentration in the agar which inhibits 99% of strain growth, is determined after 3 weeks, 4 weeks and 5 weeks after inoculation.

Pleuromutilins of the present invention show activity against strains of *Mycobacterium*, e.g. *M.tuberculosis* and are thus useful in the treatment of infectios caused by *Mycobacterium*. Pleuromutilins of the present invention surprisingly are even active against resistant and multiresistant *M.tuberculosis* strains, e.g. strains which are resistant against treatment with known pharmaceuticals useful in the treatment of tuberculosis, e.g. Isoniacid, Rifampicin, Streptomycin.

Example 1

Determination of *Mycobacterium tuberculosis* strain resistance

Activity of the known compounds Isoniacid, Rifampicin and Streptomycin against *M.tuberculosis* strains 1 to 14 as set out in TABLE 1 is determined in the Agar Dilution Test according to the method as described in the General Procedure. The MIC is determined after 3, 4 and 5 weeks. The strains 1 to 7 tested were found to be either sensible (S) or resistant (R) against Isoniacid, Rifampicin and/or Streptomycin. Results are as set out in TABLE 1 below:

TABLE 1

M.tuberculosis	**Isoniacid**	**Rifampicin**	**Streptomycin**
Strain 1	S	S	S
Strain 2	S	S	S
Strain 3	R	R	S
Strain 4	R	R	R
Strain 5	R	R	S
Strain 6	S	S	S
Strain 7	R	S	R
Strain 8	S	R	S
Strain 9	R	S	R
Strain 10	S	S	S
Strain 11	S	S	S
Strain 12	S	S	S
Strain 13	S	S	S
Strain 14	S	S	S
Strain 15	S	S	S

Strain 15 is the labor strain 137kV. Resistant and sensible strains are isolated from patients with known sensibilities/resistance. A strain is designated as resistant if its MIC in testing according to the General Test Procedure after 3 to 5 weeks is higher than 20 µg/ml.

Example 2

Activity of TEST COMPOUNDS (TCs) against *M.tuberculosis* strains 1 to 5 and 7 as set out in TABLE 1 is determined in the Agar Dilution Test under conditions as in Example 1 in different agar concentrations of the TEST COMPOUNDS.

The MIC is determined after 3, 4 and 5 weeks.

Activity of the following TEST COMPOUNDS (TC) is tested:

A compound of formula I-Tiamulin: TC-1

A compound of formula I-Valnemulin: TC-2

A compound of formula I-WO0109095: TC-3

A compound of formula II-WO0109095: TC-4

A compound of formula III-WO0109095: TC-5

Test results are as set out in TABLE 2 below are obtained:

TABLE 2

TC/week	MIC (µg/ml) against Mycobacterium tuberculosis of strain number					
	1	2	3	4	6	7
TC-1/3	5	5	5	5	10	10
TC-1/4	5	5	5	10	10	20
TC-1/5	5	5	5	10	10	20
TC-2/3	0.5	1	1	5	5	5
TC-2/4	0.5	5	1	5	5	5
TC-2/5	0.5	5	5	5	5	10
TC-3/3	1	5	5	1	5	20
TC-3/4	1	5	5	5	10	20
TC-3/5	1	5	5	10	10	20
TC-4/3	0.5	5	1	1	5	5
TC-4/4	1	5	1	5	5	5
TC-4/5	1	5	5	5	5	5
TC-5/3	1	5	5	5	5	5
TC-5/4	5	5	5	5	10	10
TC-5/5	5	5	5	10	10	10

Example 3

Is carried out according to the method of example 2. Test results obtained are as set out in TABLE 3 and in TABLE 4:

TABLE 3

TC/week	MIC (µg/ml) against Mycobacterium tuberculosis of strain number							
	1	2	3	4	5	6	7	8
TC-2/3	0.5	4	2	8	2	4	4	4
TC-2/4*)	0.5	4	2	8	4	4	8	8
TC-4/3	1	4	1	4	2	4	2	2
TC-4/4	2	4	1	4	2	4	4	2
TC-4/5	2	4	1	4	2	4	4	4

*) Tested after 31 days and thus no further testing after 5 weeks.

TABLE 4

TC/week	MIC (µg/ml) against Mycobacterium tuberculosis of strain number					
	10	11	12	13	14	15
TC-2/3	4	2	4	4	4	2
TC-2/4*)	4	4	4	8	4	4
TC-4/3	2	2	2	2	4	2
TC-4/4	2	2	2	2	4	2
TC-4/5	4	2	4	4	4	4

*) Tested after 31 days and thus no further testing after 5 weeks.

In TABLES 2 to 4 in the column "TC/week" the term "TC-number" indicates the TEST COMPOUND as defined above, e.g. TC-1 indicates a compound of formula I-Tiamulin; and "/week" indicates the MIC-determination point (in weeks from inoculation) in the testing of such TEST COMPOUND. "TC-1/3" for example indicates that the MIC of a compound of formula I-Tiamulin was determined after 3 weeks from inoculation.

MIC is the minimum inhibition concentration as defined above. The strain numbers 1 to 4 and 6 to 7 indicated in TABLE 2, the strain numbers 1 to 9 indicated in TABLE 3 and the strain numbers 10 to 15 indicated in TABLE 4 refer to the corresponding *Mycobacterium tuberculosis* strains of example 1.

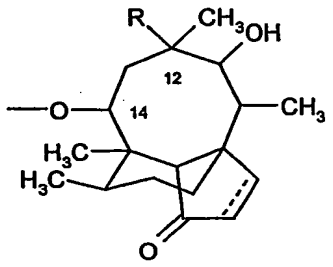
Patent Claims

1. Use of a pleuromutilin in the preparation of a medicament for the treatment of diseaeses caused by *Mycobacterium*.

2. A method of preventing or treating diseases caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective amount of a pleuromutilin.

3. Use according to claim 1 or a method according to claim 2 wherein *Mycobacterium* is *Mycobacterium tuberculosis*.

4. Use or a method according to any one of the preceding claims wherein a pleuromutilin is a compound comprising the basic structural elements as set out in formula

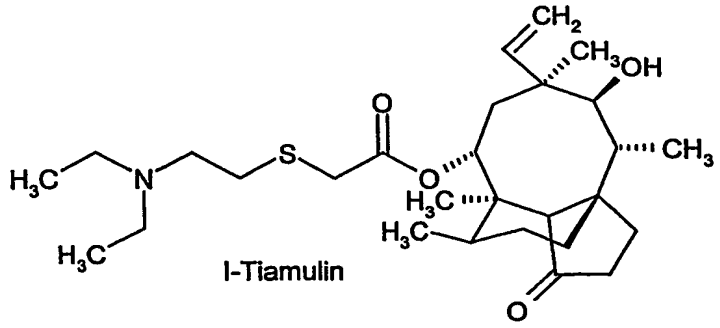


PLEU

wherein R is vinyl or ethyl and the dotted line is a bond or is no bond.

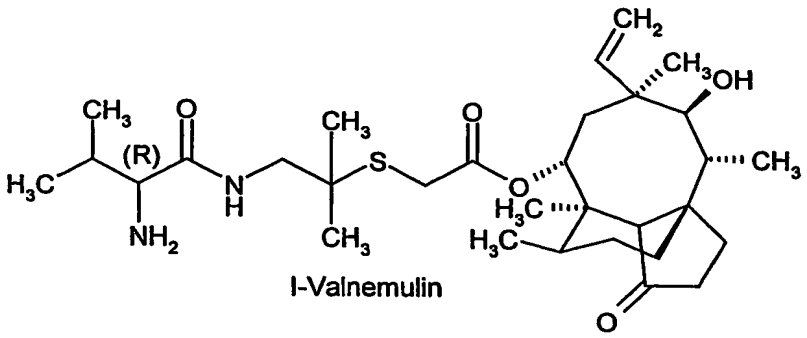
5. Use or a method according to claim 4 wherein a pleuromutilin is selected from the group consisting of

- a compound of formula



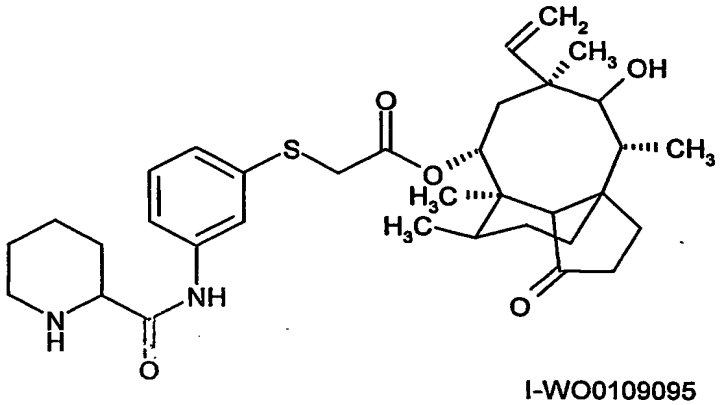
I-Tiamulin

- a compound of formula



I-Valnemulin

- a compound of formula



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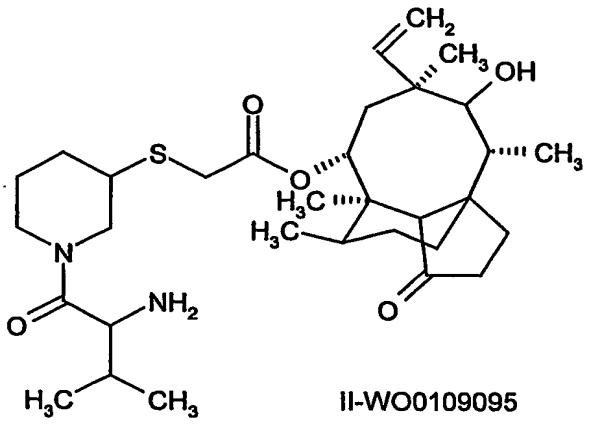
a compound of formula



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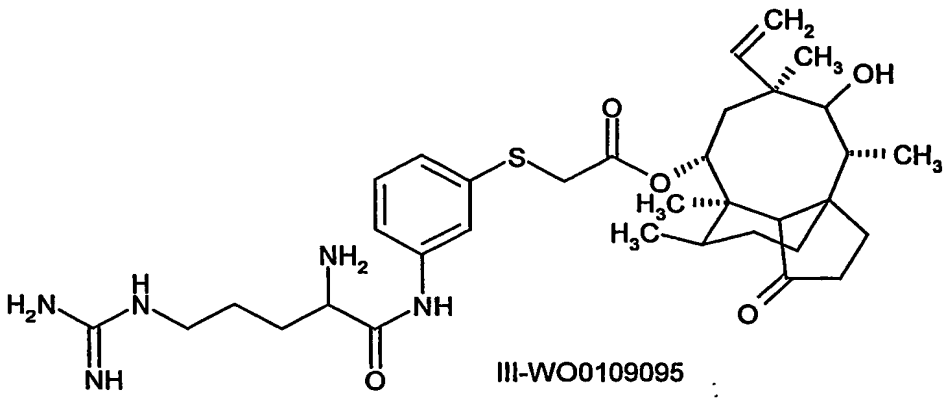
and

- a compound of formula



III-WO0109095

SC/27-Mar-02

Abstract

A method of preventing or treating diseases caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective amount of a pleuromutilin.